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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,739	03/14/2002	Masayuki Amagai	201487/1070	5390

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,739	AMAGAI ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment, response, translation of the priority document, and the Declaration of Masayuki Amagai under 37 CFR § 1.132 filed 7/21/03 have been entered and assigned as Papers # 12 and 13. Claims 2-13, 17, 19-25 have been amended. Claims 2-25 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims, the translation of the priority document, and the Declaration will not be reiterated. The arguments in paper #12 would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-25 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a rodent model showing a phenotype of pemphigus vulgaris by transplanting immune cells of the donor into an immunodeficient rodent recipient, wherein the donor lacks a gene encoding auto-antigen Dsg3, does not reasonably provide enablement for making a phenotype of *any* autoimmune disease in *any* non-human mammal by transplanting immune cells of a donor lacking a gene encoding *any* auto-antigen. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In paper #12, Applicants argue that it is not necessary to know detailed knockout phenotypes of an antigenic gene to make or use the claimed invention. Applicants indicated that in order to practice the present invention, all that is required is to obtain immune cells from a chosen characterized knockout animal, and techniques of making knockout animals have become routine in the relevant art. Applicants also cited a post-filing art as support for the availability of knockout animals.

The arguments have been fully considered but they are not persuasive for reasons of record and following.

The argument conflicts itself because the acknowledged need for using the recited "chosen characterized knockout animal" requires knowing the detailed knockout phenotype of the animal, and availability of such animal. Apparently, practicing the full scope of the claimed invention requires using a complete line of non-human animals deficient in a particular antigen associated with a particular autoimmune disease, i.e. an auto-antigen knock out non-human mammal. However, the specification fails to teach any other antigen knockout animal besides Dsg3-/- and whether such practice could be reasonably extrapolated and applied to any autoimmune disease model. As analysed in the previous action, according to the current state of the art of autoimmunity, autoantigens responsible for a particular disease is either not clearly defined or not limited to *one* particular protein. Thus, it is often unfeasible or impractical to generate an autoantigen-deleted knock-out mammal for majority of the well-known autoimmune

disease. When the antigen is known and limited to a particular cellular receptor, such as AchR for myathesnia gravis, and GpIIb:IIIa fibrinogen receptor for autoimmune thrombocytopenic purpura, the physiological consequence of knocking out the receptors and viability of the resulting mammals is unpredictable. Moreover, even if such an animal with a desired phenotype is generated and viable, it is unpredictable whether a correlating autoimmune disease phenotype could be reproduced upon transplantation of the immune cells from the knockout, because multiple factors determine the onset of an autoimmune disease.

The previous Office action particularly pointed out that although the techniques of making transgenic and knock out animals have become routine in the relevant art, the resulting *genotype and phenotype* vary significantly depending on the genes being manipulated, and the animals being used because gene manipulation and the resulting phenotype of transgenic animals is not always consistent due to reasons such as gene functional redundancy and species difference, and that homozygous transgenic animal may not be viable. Further, it is highly unpredictable to extrapolate from the rodent study to any non-human animal particularly large animals as taught by *Mullins et al* and *Linder*. It is also necessary to reiterate that *Logan and Sharma* (Clin Exp Pharmacol Physiol 1999 Dec;26:1020-25) teach "THE CHALLENGE IN THE DEVELOPMENT OF TRANSGENE IS NOT IN THIS PROCESS, BUT IN THE DESIGN OF THE CONSTRUCT THAT WILL ALLOW FOR THE EXPRESSION OF THE GENE OF INTEREST IN THE DESIRED CELL TYPE AT AN APPROPRIATE LEVEL", "PROBLEMS WITH OBTAINING EXPRESSION OF TRANSGENES IN ANIMALS HAVE BEEN RELATED TO THE INABILITY TO ROUTINELY OBTAIN HIGH LEVELS OF EXPRESSION, ESPECIALLY OVER MULTIPLE GENERATIONS, AND THE OBSERVATION OF VARIEGATED EXPRESSION, WHEREBY NOT ALL CELLS IN AN

ORGAN WILL EXPRESS THE GENE. *Pearson* (Nature 2002;415:8-9) comments, "INDEED, CLEAR AND CONSISTENT PHENOTYPES NOW SEEM TO BE THE EXCEPTION RATHER THAN THE RULE" (left column, page 8). Accordingly, the phenotypes resulting from homozygous knock out of a particular antigen are expected to be varied and unpredictable. The skilled artisan could not practice the invention without first carrying out undue experimentation to make a homozygous knockout for any particular gene encoding an auto-antigen.

The newly submitted publication of *Marians et al* could not support the enablement of instantly claimed invention, because the specification fails to teach the thyrotropin receptor-null mice at the time of the filing, and the enablement of the instant disclosure could not relied on a post-filing date publication. The court has stated (*In re Glass*, 181 USPQ 31, (CCPA 1974)), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. The fact that the specific protocol is not disclosed in the specification indicates that the specification does not support the claims as filed, but instead reflects further critical information that is essential for the artisan to practice the invention.

Furthermore, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). In applications directed to inventions in arts where the results are unpredictable, the

disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT." Accordingly, the instant disclosure is insufficient to support the full scope of the claims because the disclosure only enables making and using a rodent model of pemphigus vulgaris.

For reasons of record and set forth above, the rejection stands.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
October 1, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER